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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/713,929	11/14/2003	Gopi Venkatesh	EURA-004/00US 307853-2001	4820

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EXAMINER	
BARHAM, BETHANY P	

ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/713,929	VENKATESH ET AL.	
	Examiner	Art Unit	
	Bethany P. Barham	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-11,24 and 25 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-11,24 and 25 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Upon further consideration resulting from the pre-appeal brief conference (08/02/07), prosecution has been re-opened. The previous rejections of record (06/13/07) are hereby **withdrawn**. Claims 1-11 and 24-25 are pending. Claims 1-11 and 24-25 are rejected.

NEW REJECTIONS:

Claim Rejections – 35 USC §112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 and 24-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a specific drug, specific water soluble polymer, specific plasticizer, and specific water insoluble polymer, does not reasonably provide enablement for any and all water insoluble polymers, plasticizers and water soluble polymers. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. Original claims 7, 9, and 11 might describe water soluble and insoluble polymers, and plasticizers, which could lead to claim 1. However, claim 1 describes any water insoluble polymer, does not need a

plasticizer or a water soluble polymer, and the claim is directed to function not structure. Based on claims 7, 9, and 11 more than just any water insoluble polymer is needed for claim 1. One is then invited to experiment to obtain claim 1 to determine what specific water insoluble polymers are used and what other components are needed. The difference between independent claim 1 and dependent claims 7-11 is that 7,9 and 11 are limited to a specific subset of water soluble polymers, plasticizers, and water insoluble polymers versus claims 1-6, 8, 10 and 24-25, in which all are possible.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: (1) breadth of the claims; (2) nature of the invention; (3) state of the prior art; (4) amount of direction provided by the inventor; (5) the level of predictability in the art; (6) the existence of working examples; (7) quantity of experimentation needed to make or use the invention based on the content of the disclosure; and (8) relative skill in the art. All of the factors have been considered with regard to the claim, with the most relevant factors discussed below:

The breadth of claims: The instant claim 1 is directed to a multi-particulate dosage form comprising "wherein said extended release beads comprise an active-containing core particle...of cyclobenzaprine; an extended release coating comprising a water insoluble polymer membrane surrounding said core" and further a specific dissolution profile:

> USP Apparatus 2 (paddles @ 50 rpm) in 900 mL of 0.1N HC1 at 37°C exhibits a drug release profile substantially corresponding to the following pattern:

after 2 hours, no more than about 40% of the total active is released;

after 4 hours, from about 40-65% of the total active is released;

and after 8 hours, from about 60-85% of the total active is released;

and after 12 hours, from about 75 85% of the total active is released;

wherein said dosage form provides therapeutically effective plasma concentration over a period of 24 hours to treat muscle spasm associated with painful musculoskeletal conditions when administered to a patient in need thereof.

It is the examiner's position that this claim is not supported by the instant specification, because Examples and dependent claims 7, 9, and 11 require a specific water insoluble polymer, specific plasticizer and a specific water soluble polymer.

The nature of the invention: The instant invention is directed to a multi-particulate dosage form comprising "wherein said extended release beads comprise an active-containing core particle...of cyclobenzaprine; an extended release coating comprising a water insoluble polymer membrane surrounding said core".

The state of the prior art: As set forth in Meadows et al US 2003/0099711 A1; a composition of their invention can be coated with a water-permeable diffusion barrier coating that is insoluble in gastrointestinal fluids thereby providing a controllable sustained release of drug and/or an enteric coating to formulate tailored release profiles [0001, 0009-0010, 0023]. Meadows et al teaches that the invention provides

therapeutic levels of the drug throughout the day and a controlled release drug preparation delivers drugs in a manner that will maintain therapeutically effective plasma levels over a period of time that is significantly longer than that which is given by a typical drug dosage form [0002]. Meadows et al teaches that cyclobenzaprine is a suitable drug for their composition ([0029], col. 2 and claim 13). Meadows et al teaches coating with a diffusion barrier, preferably ethyl cellulose, such as Aquacoat or Surelease [0040, 0042-0043] and/or enteric coatings to allow the active ingredients to be released once the dosage has passed into the small intestinal tract [0046]. The enteric coating include copolymers of methacrylic acid and methyl methacrylate or ethyl acrylate, terpolymers of methacrylic acid, methacrylate, and ethyl acrylate [0047]. Meadows et al teach that it is possible to tailor the drug release properties of the pharmaceutical preparation to provide a desired bioavailability profile, such as enteric coated free drug adsorbed on an inert substrate [0062-0067]. Meadows et al found that the enteric coated particles provide release in vivo of at least one drug over a period of about 4 hours, preferably over a period of 12 hours and more preferably the formulations of the present invention release in vivo at least one drug over a period of 24 hours ([0070] and claims 1, 8, 30 and 37-39). The art suggests that the parameters of coating, etc are varied depending upon the dissolution profile desired.

The amount of direction provided by the inventor: There is nothing in the specification that would indicate that the current invention is any different than that of the prior art. With respect to the instant composition, there is a substantial gap between

a composition comprising a specific active agents and a water insoluble polymer and one comprising a specific water insoluble polymer, specific plasticizer and a specific water soluble polymer. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap.

The presence or absence of working examples: There are examples in the instant specification, which describe the process of making a dosage form of claimed invention, by coating beads with the drug, adding a seal coat and further an enteric coating layer for extended release. All examples refer to a multi-particulate dosage form, and one comprising a specific water insoluble polymer (ethyl cellulose or Aquacoat), specific plasticizer (dibutyl sebacate or diethyl phthalate) and a specific water soluble polymer (polyvinylpyrrolidone), all of which are also taught and claimed by Meadows et al.

The quantity of experimentation: In the instant case, there is a substantial gap between a composition comprising a cyclobenzaprine and a water insoluble polymer and one comprising a specific water insoluble polymer, specific plasticizer and a specific water soluble polymer. Consequently, a burdensome amount of research would be required by one of ordinary skill in the art to bridge this gap. In order to utilize the invention as claimed, the skilled artisan would be presented with an unpredictable amount of experimentation. It is not clear what specific embodiments would be required in order for one of ordinary skill in the art at the time the invention was made to practice the instant invention commensurate in scope with the claims.

The relative skill of those in the art: the skill of one of ordinary skill in the art is very high, e.g., Ph.D. and M.D. level technology.

Claim Rejections – 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-11 and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al US 2003/0215496 A1.

Patel et al teach the limitations of claims 1-7 and 24:

- Patel et al teaches a composition comprising muscle skeletal relaxants and cyclobenzaprine, salts, isomers and derivatives and mixtures thereof ([0036] and claim 24).
- Patel et al teaches compositions that can be provided in the form of a minicapsule, a capsule, tablet,....a pellet, a bead, etc ([0168] and claims 5-7, 52). Examples 1-5 teaches how to prepare active ingredient coated beads.
- Pharmaceutical composition and/or the solid carrier particles taught by Patel et al can be coated with one or more enteric coatings, seal coatings, film coatings, barrier coatings, etc., and that the dosage form can be designed for immediate

release, pulsatile release, controlled release, extended release, delayed release, targeted release, synchronized release, or targeted delayed release ([0169, col. 1] and claims 1, 53, and 59-60). Patel et al also teaches that the dosage form release profile can be affected by a polymeric matrix composition, a coated matrix composition, a multiparticulate composition, a coated multiparticulate composition, etc [0169, col. 2].

- The extended release coatings of Patel et al are preferably pH-independent coatings formed of, for example, ethyl cellulose [0172] and delayed release enteric coatings are acrylic polymers methacrylic acid copolymers, ammonio methacrylate copolymers, the Eudragit series E, L, S, RL, RS, NE and L-30D, and ethyl cellulose ([0184-0185], Example 8).

Patel et al teach the limitations of claims 8-9:

- Patel et al teaches that the coating can and usually does contain a plasticizer such as: triethyl citrate triacetin, acetyl triethyl citrate, polyethylene glycol 400, diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol and dibutyl phthalate [0189].

Patel et al teaches the limitations of claim 10-11:

- Patel et al teaches that various extended release dosage forms can be readily designed by one skilled in the art to achieve delivery to both the small and large intestines, to only the small intestine or to only the large intestine, depending on the choice of coating materials and/or coating thickness [0172].

- Extended release coatings of Patel et al also teach water soluble polymers such as hydroxypropyl cellulose, methylcellulose, hydroxymethyl cellulose, acrylic esters, etc. [0172].
- Patel et al does not teach the specific drug release profiles and concentrations as claimed by applicant, but teaches the same coatings, coating thickness and drug as instant claimed and that one of ordinary skill in the art would know how to obtain a dosage with a desired performance, specifically extended release ([0169, 0172] claims 59-60).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to look to Patel et al to make an extended release dosage form of cyclobenzaprine. Patel et al teaches various drugs including cyclobenzaprine coated enterically onto beads for extended release. One of ordinary skill in the art would be motivated to obtain specific release profiles and dissolution since Patel et al teaches that one of ordinary skill in the art would know how to vary the coatings and dosage form to obtain a desired performance.

Claims 1-4, 6-11 and 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meadows et al US 2003/0099711 A1.

Meadows et al teaches the limitations of claim 1-4, 6-7 and 24:

- Meadows et al teaches that the composition of their invention can be coated with a water-permeable diffusion barrier coating that is insoluble in gastrointestinal

fluids thereby providing a controllable sustained release of drug and/or an enteric coating to formulate tailored release profiles [0001, 0009-0010, 0023]. Meadows et al teaches that the invention provides therapeutic levels of the drug throughout the day and a controlled release drug preparation delivers drugs in a manner that will maintain therapeutically effective plasma levels over a period of time that is significantly longer than that which is given by a typical drug dosage form [0002].

- Meadows et al teaches that cyclobenzaprine is a suitable drug for their composition ([0029], col. 2 and claim 13).
- Meadows et al teaches coating with a diffusion barrier, preferably ethyl cellulose, such as Aquacoat or Surelease [0040, 0042-0043] and/or enteric coatings to allow the active ingredients to be released once the dosage has passed into the small intestinal tract [0046]. The enteric coating include copolymers of methacrylic acid and methyl methacrylate or ethyl acrylate, terpolymers of methacrylic acid, methacrylate, and ethyl acrylate [0047].
- Meadows et al teach that it is possible to tailor the drug release properties of the pharmaceutical preparation to provide a desired bioavailability profile, such as enteric coated free drug adsorbed on an inert substrate [0062-0067]. Meadows et al found that the enteric coated particles provide release in vivo of at least one drug over a period of about 4 hours, preferably over a period of 12 hours and more preferably the formulations of the present invention release in vivo at least one drug over a period of 24 hours ([0070] and claims 1, 8, 30 and 37-39).

Meadows et al teaches the limitations of claim 8-9:

- Plasticizers are generally used for coating containing film-formers such as ethyl cellulose [0040]. Examples of suitable plasticizers for ethyl cellulose are dibutyl sebacate, diethyl phthalate, triethyl citrate, tributyl citrate, triacetin, acetylated monoglycerides, phthalate esters, castor oil, etc. [0041].

Meadows et al teaches the limitations of claim 10-11:

- The optimum coat weight and thickness for barrier coating materials is taught by Meadows et al to be determined specifically for each drug-resin complex. For drug release from about 1-4 hours the coat weight is present in amount of about 10-20% by weight of the dry resin. For drug release from about 6-10 hours the coat weight is present in amount of about 30-35% by weight of the dry resin, etc. [0044]. Meadows et al teaches that the water-permeable, film-forming polymer comprises from about 1 to about 60% by weight of the drug-resin complex (claim 1). For the enteric coating (claim 14) taught by Meadows et al it may be desirable to provide the coating directly onto the drug-resin complex or on a drug adsorbed on an inert substrate such as sugar spheres in the amounts of about 1.5- about 30%, preferably about 5- about 15% by weight of the particle being coated [0048].
- Water-soluble substances are taught by Meadows et al as desirable to incorporate into the coating in order to alter permeability [0041]. Such substances are HPMC, HEC, methylcellulose or other cellulose polymers or mixtures of polymers [0040].

- Meadows et al does not teach the specific drug release profiles and concentrations as claimed by applicant, but teaches the same coatings, coating thickness and drug as instant claimed and that one of ordinary skill in the art would obtain dosage form with a tailored release profile (abstract) to provide a desired bioavailability and drug release for over a period of 24 hours ([0062, 0070] claims 8 and 39).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to look to Meadows et al to make an extended release dosage form of cyclobenzaprine. Meadows et al teaches various drugs including cyclobenzaprine coated enterically onto beads for controlled release in vivo of a drug for over a period of 24 hours. Meadows et al teaches in their examples (example 5) that dissolution of the formulations of the invention can be formulated to selectively release a specific amount of drug. One of ordinary skill in the art would be motivated to obtain specific release profiles and dissolution since Meadows et al teaches that one of ordinary skill in the art would know how to vary the coatings and dosage form to obtain a desired performance.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bethany P. Barham whose telephone number is 571-272-6175. The examiner can normally be reached on M-F from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

B.P. Barham
Examiner 1615

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